

# Oxytocin Reduces Reward-Driven Food Intake in Humans

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Experiments in animals suggest that the neuropeptide oxytocin acts as an anorexigenic signal in the central nervous control of food intake. In humans, however, research has almost exclusively focused on the involvement of oxytocin in the regulation of social behavior. We investigated the effect of intranasal oxytocin on ingestion and metabolic function in healthy men. Food intake in the fasted state was examined 45 min after neuropeptide administration, followed by the assessment of olfaction and reward-driven snack intake in the absence of hunger. Energy expenditure was registered by indirect calorimetry, and blood was repeatedly sampled to determine concentrations of blood glucose and hormones. Oxytocin markedly reduced snack consumption, restraining, in particular, the intake of chocolate cookies by 25%. Oxytocin, moreover, attenuated basal and postprandial levels of adrenocorticotropic hormone and cortisol and curbed the meal-related rise in plasma glucose. Energy expenditure and hunger-driven food intake as well as olfactory function were not affected. Our results indicate that oxytocin, beyond its role in social bonding, regulates nonhomeostatic, reward-related energy intake, hypothalamic-pituitary-adrenal axis activity, and the glucoregulatory response to food intake in humans. These effects can be assumed to converge with the psychosocial function of oxytocin and imply possible applications in the treatment of metabolic disorders. *Diabetes* 62:3418–3425, 2013

**T**he hypothalamic nonapeptide oxytocin is released into the circulation by axonal terminals in the posterior pituitary and, moreover, acts directly on central nervous receptors. Oxytocin, which has been highly preserved during mammalian evolution, regulates physiological functions related to reproduction and mother-infant interaction, such as lactation, and in recent years, has been shown to modulate affiliative behavior (1). Research in humans has almost exclusively focused on the role of oxytocin in the regulation of prosocial behavior, including trust, attachment, and sexual behavior (2–5), largely ignoring potential effects of the neuropeptide on ingestive behavior and metabolism. In

fact, evidence from rodent studies indicates that the neuropeptide acts as a strong inhibitor of food intake and affects energy expenditure and glucose homeostasis (6–9). Oxytocinergic neurons in the hypothalamic paraventricular nucleus are assumed to mediate the food intake-limiting effect of leptin, an adipokine that provides the brain with negative feedback on body fat stores and sensitizes caudal brainstem nuclei to satiety factors such as cholecystokinin (10). Hypothalamic oxytocin signaling, moreover, mediates anorexigenic effects of the satiety factor nesfatin-1 in a leptin-independent manner (11). Importantly, oxytocin reduces food intake not only in normal-weight rodents but also in animals with diet-induced obesity (8,12,13), so oxytocinergic pathways might be a promising target of clinical interventions in obese patients.

The direct manipulation of neuropeptidergic central nervous signaling pathways can be achieved via the intranasal administration of peptides, which is known to bypass the blood–brain barrier and result in significant cerebrospinal fluid elevations in substance levels within 40 min, without the need for systemic infusion (14,15). This approach has been validated, among others, for vasopressin, a close homolog of oxytocin (14), and intranasal oxytocin administration has been shown to reliably modulate neuropsychological functions in a series of studies (2–5) in the absence of relevant side effects (16). Surprisingly, however, the effect of intranasal oxytocin on energy metabolism, including ingestive behavior, has not been investigated in humans so far. The assessment of respective effects of intravenous oxytocin (17) is hampered because peripheral oxytocin is not readily transported across the blood–brain barrier (18).

In the present experiments, we studied the contribution of oxytocin signaling to the control of ingestive behavior and energy expenditure in normal-weight, healthy men, with a particular view to endocrine regulators of metabolism, such as ghrelin and insulin, as well as hypothalamic-pituitary-adrenal (HPA) axis secretory activity. Ingestive behavior is not only regulated homeostatically (i.e., by central nervous pathways that respond to energy depletion) but also by nonhomeostatic brain circuits that process the reward-related, “hedonic” qualities of food intake (19). Therefore, we applied a twofold assessment of food intake that relied, on the one hand, on a large breakfast buffet after an overnight fast to investigate homeostatic, primarily hunger-driven energy intake (20–22), and on the other hand, on a collection of snacks of varying palatability offered after breakfast intake for the measurement of reward-driven food intake (22–24).

## RESEARCH DESIGN AND METHODS

**Subjects.** The study participants were 20 healthy, male, nonsmokers who were free of medication (aged  $26.3 \pm 0.89$  years; BMI  $22.66 \pm 0.36$  kg/m<sup>2</sup>). All relevant illness was excluded by medical history and clinical examination.

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Subjects were kept unaware of the hypothesized treatment effects on food intake and were informed that the experiments concerned the effect of oxytocin on taste preferences and energy expenditure. Participants gave written informed consent to the study that conformed to the Declaration of Helsinki and was approved by the local ethics committee.

**Design and procedure.** Experiments were carried out in a double-blind, cross-over, within-subject comparison. Each subject participated in two experimental sessions, oxytocin and placebo. The order of conditions was balanced across subjects, and the two sessions were spaced at least 10 days apart. Participants were instructed to abstain from the intake of food and of caffeinated and alcoholic beverages after 2000 h on the day preceding each session.

After the subject's arrival at the laboratory at ~0800 h, a venous cannula was inserted into the subject's nondominant arm to enable drawing of venous blood (see Fig. 1 for the experimental procedure). Thereafter, blood was sampled for baseline assessments of hormonal parameters. Mood, hunger, and thirst were rated, and energy expenditure was measured by indirect calorimetry. At 0942 h, six 0.1-mL puffs (three per nostril) of oxytocin (Syntocinon; Defiante Farmaceutica, Funchal Madeira, Portugal) and vehicle, respectively, were intranasally administered at 30-second intervals, amounting to a total dose of 24 IU oxytocin (0.6 mL).

Forty-five minutes after administration, subjects were presented with a breakfast buffet from 1030–1100 h. Olfactory function was tested at 1155 h. Mood, hunger, and thirst were rated, and energy expenditure was measured by indirect calorimetry after substance administration and after the breakfast buffet (Fig. 1). At 1240 h, casual snack intake was assessed under the pretext of a snack taste test. At 60 min before and at 35 and 120 min after substance administration, subjects rated the experimenter's general trustworthiness. Heart rate and blood pressure were monitored throughout the experiment. At the end of the experiments, subjects were asked to indicate their account of the study purpose.

**Assessments of food intake, hunger, thirst, mood, and olfaction.** The free-choice ad libitum test buffet comprised a variety of food choices (Table 1) from which subjects could eat undisturbed for 30 min. They were not aware that their food intake was measured by weighing buffet components before and after breakfast. This procedure has been repeatedly shown to enable the precise assessment of primarily hunger-driven food intake in the fasted state (20–22). Reward-related eating in the absence of hunger was assessed using a snack test validated in a series of previous studies (22–24). Subjects were presented with three types of snacks of different taste but comparable calorie content and macronutrient composition (Table 2), each on a separate plate, and labeled snack A, B, and C, respectively. The three types were, "TUC Cracker Classic" (salty taste; Griesson-de Beukelaer, Polch, Germany), "Rice Waffles" (bland taste; Continental Bakeries B.V., Dordrecht, The Netherlands), and "Double Chocolate Cookies" (sweet taste; EDEKA, Hamburg, Germany). For each variety, 15 snacks broken into bite size pieces were provided, allowing for a considerable amount to be eaten without the plates appearing empty to ensure that participants would not restrict snack intake based on

whether the experimenter could see how much had been consumed. The participant was instructed to taste and rate each type of snack on a visual analog scale (VAS) anchored by 0 (not at all) and 10 cm (very palatable/sweet/salty). The importance of giving accurate ratings was emphasized, and subjects were informed that during and after completion of the rating task they could eat as many snacks as they liked because any remaining food would be discarded, and were left alone for 10 min. Snack intake was covertly measured by weighing the snacks before and after the test.

Hunger, thirst, and also trustworthiness of the experimenter were rated on VAS (0–100 mm). Self-reported mood was assessed with 5-point scales covering the categories good/bad mood, alertness/sleepiness, and calmness/agitation (*Der mehrdimensionale Befindlichkeitsfragebogen* [25]). Olfactory function was tested 60 min after the test buffet with the validated Sniffin' Sticks commercial test kit (Burghart Elektro- und Feinmechanik GmbH, Wedel, Germany) that allows for the separate characterization of the three dimensions of olfactory threshold, discrimination, and identification (26).

**Measurement of energy expenditure, plasma glucose, and hormonal parameters.** Energy expenditure (expressed as kcal/day) was measured via indirect calorimetry using a ventilated-hood system (Deltatrac II, MBM-200 Metabolic Monitor; Datex-Engström Deutschland, Achim, Germany). Before each use, the device was calibrated with Quick Cal calibration gas to 5% CO<sub>2</sub> and 95% O<sub>2</sub>. Calorimetric measurements took place from 0900 to 0930 h (baseline), immediately after intranasal substance administration from 0945 to 1015 h to assess effects of intranasal oxytocin alone, and again between 1105 and 1145 h (i.e., after the ad libitum test buffet) to register postprandial energy expenditure. The rise in energy expenditure between the fasting state (baseline) and the postprandial state reflects diet-induced thermogenesis (i.e., the energy that is emitted as heat during metabolism of food) and thus does not contribute to the production of ATP (27).

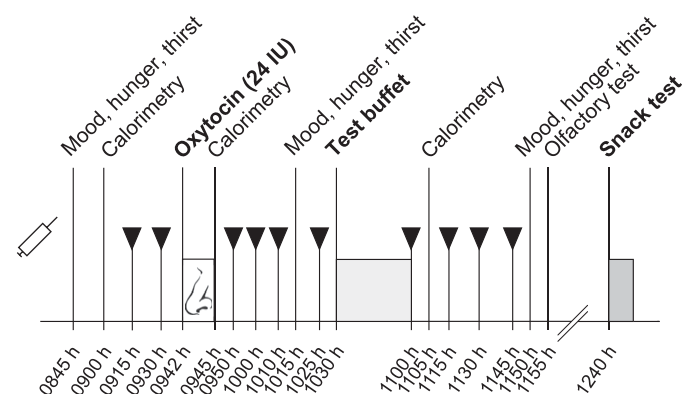
Blood samples for the assessment of serum insulin, C-peptide, cortisol, growth hormone, leptin, plasma glucose, glucagon, total and active glucagon-like peptide-1 (GLP-1), adrenocorticotrophic hormone (ACTH), and total ghrelin were centrifuged, and samples were stored at –80°C. Blood for the measurement of glucagon and total/active GLP-1 was pretreated with aprotinin (370 kIU/mL; Roth GmbH, Karlsruhe, Germany) and dipeptidyl peptidase-IV-inhibitor blocking reagent (50 µmol/L; Millipore, St. Charles, MO), respectively. Routine assays were used to determine concentrations of plasma glucose measured in fluoride plasma according to the hexokinase method (Aeroset; Abbott Diagnostics, North Chicago, IL), insulin, C-peptide, ACTH, cortisol (all Immulite, DPC, Los Angeles, CA), total ghrelin, leptin, total and active GLP-1 (all RIA, Millipore, Billerica, MA), and glucagon (RIA, IBL International, Hamburg, Germany).

**Statistical analysis.** Analyses were based on ANOVA with the within-subject factors "treatment," "time," "nutrient," and "snack type," as appropriate. Degrees of freedom were corrected using the Greenhouse-Geisser procedure. Significant ANOVA effects were specified by pairwise *t* tests. For blood parameters and energy expenditure, baseline adjustment was achieved by subtracting individual baseline values from individual postintervention measurements. Supplementary analyses of snack intake and blood glucose peak values relied on ANCOVA, including as covariates the differences between conditions in overall calorie and carbohydrate consumption during breakfast intake. All data are presented as means ± SEM. A *P* value < 0.05 was considered significant.

## RESULTS

**Oxytocin inhibits reward- but not hunger-driven eating.** Oxytocin administration did not affect food intake from the breakfast buffet in the fasted state. Overall food consumption and the proportion of ingested macronutrients were nearly identical between conditions (all *P* > 0.6; Table 3). Accordingly, hunger ratings (*P* > 0.2, two-sided *t* test for baseline values; Fig. 2A) were not altered by oxytocin (*P* > 0.9) and fell to comparably low values of ~15% of the maximal score during breakfast (*P* > 0.2;  $F_{2,36} = 74.91$ , *P* < 0.0001 for time; *P* > 0.5 for treatment effects), indicating that subjects in both conditions were satiated by breakfast intake. Thirst ratings and self-rated mood were likewise unaffected by oxytocin (*P* > 0.12 for all comparisons).

In the snack test during the postprandial period, oxytocin compared with placebo induced a reduction in total snack intake ( $F_{1,19} = 5.5$ , *P* < 0.03 for treatment; Fig. 2B)



**FIG. 1.** Experimental procedure. After baseline assessments of blood parameters, psychological variables and energy expenditure, healthy young men were intranasally administered oxytocin (24 IU) and placebo, respectively, at 0942 h (nose symbol). At 1030 h, 45 min after substance administration, subjects were allowed to eat ad libitum from a free-choice test buffet for 30 min. At ~60 min after termination of the buffet, at 1155 h, olfactory function was assessed, and at 1240 h, 100 min after the end of the buffet meal, snack intake was measured under the pretext of a taste-rating task. Throughout the session, mood, hunger, and thirst were assessed, and blood samples were taken (▼).

TABLE 1  
Composition of the test buffet

Food	Weight (g)	Energy (kcal)	Carbohydrate (g)	Fat (g)	Protein (g)
Neutral					
Whole wheat bread	165	360	71	2.3	12
Wheat rolls	240	275	122.4	3.4	6.3
White bread	30	72	14.6	0.4	2.2
Butter	120	928	0.7	99.8	0.8
Whole milk	750	491	36	26.3	24.8
Sweet					
Strawberry jam	50	147	35.8	0.1	0.1
Hazelnut spread	40	218	21.6	12.8	2.8
Honey	40	123	30	0	0.1
Sugar	24	98	24	0	0
Fruit curd	125	140	19.3	3.3	7.7
Vanilla pudding	125	134	20.8	3.8	3.5
Strawberry milk	200	167	18.2	6.8	7.4
Banana	179	168	38.3	0.4	2
Apple	195	104	22.2	1.2	0.6
Pear	140	78	17.4	0.4	0.7
Orange	180	72	15	0.4	1.8
Tangerine	80	35	8.2	0	0.5
Orange juice	400	173	36	1	4
Savory					
Poultry sausage	40	74	0.1	4.3	8.3
Cervelat sausage	34	120	0.1	10.2	6.1
Sliced cheese	100	374	0	29.2	25.5
Cream cheese (natural)	33	87	0.6	7.8	3
Cream cheese (herbs)	40	124	1	11.6	3.2
Total	3,330	4,562	553	226	123

All values are rounded to the closest decimal.

that was driven by a decrease in chocolate cookie consumption by 25% ( $P < 0.01$ , two-sided  $t$  test; Fig. 2C and Table 4). These effects remained significant when corrected for overall calorie and carbohydrate consumption during the preceding test buffet (both  $P < 0.04$  for treatment;  $P < 0.007$  for the difference in chocolate cookie consumption). Across conditions, intake of chocolate cookies by far exceeded that of the remaining snacks ( $F_{1,23} = 9.50$ ,  $P < 0.004$  for snack type). Also, sweetness and saltiness ratings were highest for chocolate cookies and salt crackers, respectively ( $F_{2,31} = 342.28$ ,  $P < 0.0001$ ; and  $F_{2,36} = 112.18$ ,  $P < 0.0001$ , for snack type). Oxytocin did not affect ratings for chocolate cookies and salt crackers ( $P > 0.3$ ) and even slightly increased rated palatability of rice waffles ( $P < 0.05$ ; Table 4). In the olfactory task, no treatment effects on perceptual thresholds ( $P > 0.4$ ), olfactory discrimination ( $P > 0.6$ ), and olfactory identification ( $P > 0.2$ ) emerged, and oxytocin administration did not affect the trustworthiness of the experimenter as perceived by the participants ( $P > 0.6$ ).

**Energy expenditure is not acutely affected by oxytocin administration.** Energy expenditure assessed by indirect calorimetry was comparable between the placebo and the oxytocin condition during the entire experimental period ( $F_{1,19} = 2.12$ ,  $P > 0.16$  for treatment  $\times$  time;  $F_{1,19} = 0.10$ ,  $P > 0.75$  for treatment), averaging  $1609 \pm 41$  vs.  $1651 \pm 37$  kcal/day ( $P > 0.12$ ) under baseline fasting conditions,  $1615 \pm 21$  vs.  $1633 \pm 13$  kcal/day ( $P > 0.46$ ) after placebo and oxytocin administration, respectively, and  $2021 \pm 48$  vs.  $1985 \pm 34$  kcal/day ( $P > 0.4$ ) after breakfast intake, with the latter values reflecting diet-induced thermogenesis  $\sim 23\%$  above preprandial baseline measurements ( $F_{1,19} = 145.24$ ,  $P < 0.0001$  for time).

**Oxytocin reduces HPA axis activity as well as norepinephrine concentrations and blunts the glucose response to food intake.** During baseline, none of the blood parameters, including blood glucose, differed between conditions (all  $P > 0.18$ ). Oxytocin exerted a sustained suppressive effect on HPA axis activity, reducing serum ACTH and plasma cortisol concentrations during the entire postadministration period ( $F_{1,18} = 4.67$ ,  $P < 0.05$  and  $F_{1,18} = 5.15$ ,  $P < 0.04$ , respectively, for treatment; Fig. 2D and E). The effect on cortisol was particularly pronounced before breakfast intake ( $F_{2,35} = 4.82$ ,  $P < 0.02$  for treatment  $\times$  time). In parallel, preprandial circulating concentrations of norepinephrine were reduced by oxytocin treatment ( $F_{1,19} = 5.41$ ,  $P = 0.03$  for treatment  $\times$  time; Fig. 3F). Supplementary analyses indicated that the oxytocin-induced decreases in cortisol concentrations (area under the curve with respect to increase 0930–1145 h) and chocolate cookie intake were

TABLE 2  
Snacks offered in the snack test

	Chocolate cookies	Rice waffles	Salt crackers
Energy value (kcal/100 g)	500	390	486
Carbohydrate (g/100 g)	57.2	63	63
Fat (g/100 g)	26.6	22	22
Protein (g/100 g)	6	8.6	7.8

Nutritional values of the snacks offered to the participants during the postprandial period. All values are according to the manufacturers' data (see RESEARCH DESIGN AND METHODS). A glass of still mineral water was provided along with the cookies.

TABLE 3  
Food intake from the test buffet

Food intake (kcal)	Placebo	Oxytocin	<i>P</i> value
Total	1,180 ± 103	1,190 ± 105	0.84
Carbohydrates	517 ± 41	540 ± 41	0.43
Fat	517 ± 54	509 ± 57	0.84
Protein	145 ± 16	142 ± 14	0.82
Savory foods	314 ± 38	309 ± 29	0.91
Sweet foods	233 ± 44	206 ± 40	0.22

Total food intake, intake of macronutrients, and food intake according to taste. Savory and sweet foods contained in the test buffet are listed separately in Table 1. *P* values are derived from paired, two-tailed *t* tests (*n* = 20).

significantly correlated ( $r = 0.56$ ;  $P = 0.012$ , Pearson's coefficient).

The circulating concentrations of glucose, insulin, C-peptide, and total GLP-1 showed the expected meal-related increase across conditions (all  $P < 0.0001$  for time; Fig. 3A–D). Although levels of insulin, C-peptide, and total GLP-1 were not affected by oxytocin administration (all  $P > 0.16$ ), the peak glucose response to breakfast intake (15 min after meal termination) was reduced by 0.57 mmol/L after oxytocin compared with placebo administration

( $P < 0.02$ , two-sided *t* test; Fig. 3A). This difference was still evident when adjusted for preceding total and carbohydrate-specific breakfast intake (both  $P < 0.03$ ). Total plasma concentrations of ghrelin were suppressed by breakfast intake ( $F_{2,29} = 31.62$ ,  $P < 0.0001$  for time), without significant treatment effects ( $P > 0.95$ ; Fig. 3E). Conversely, 15 min after breakfast, serum leptin levels were increased by ~28% compared with preprandial levels ( $F_{4,80} = 28.98$ ,  $P < 0.0001$  for time; Fig. 3F). Leptin concentrations did not differ between conditions across the whole experimental period ( $P > 0.38$ ), although there was a trend toward reduced preprandial leptin concentrations after oxytocin administration ( $F_{1,19} = 3.39$ ,  $P = 0.08$  for treatment). Circulating concentrations of growth hormone and active GLP-1 (i.e., the intact form of GLP-1) were likewise comparable between conditions (all  $P > 0.14$ ).

## DISCUSSION

We demonstrate that oxytocin inhibits food intake and impacts endocrine regulation in humans. The anorexigenic effect of oxytocin emerged during the postprandial period, when reward-driven eating motivation prevails, whereas energy intake in the fasted state was not affected. Although this pattern could also imply that oxytocin effects on ingestive behavior emerge with a certain delay, this

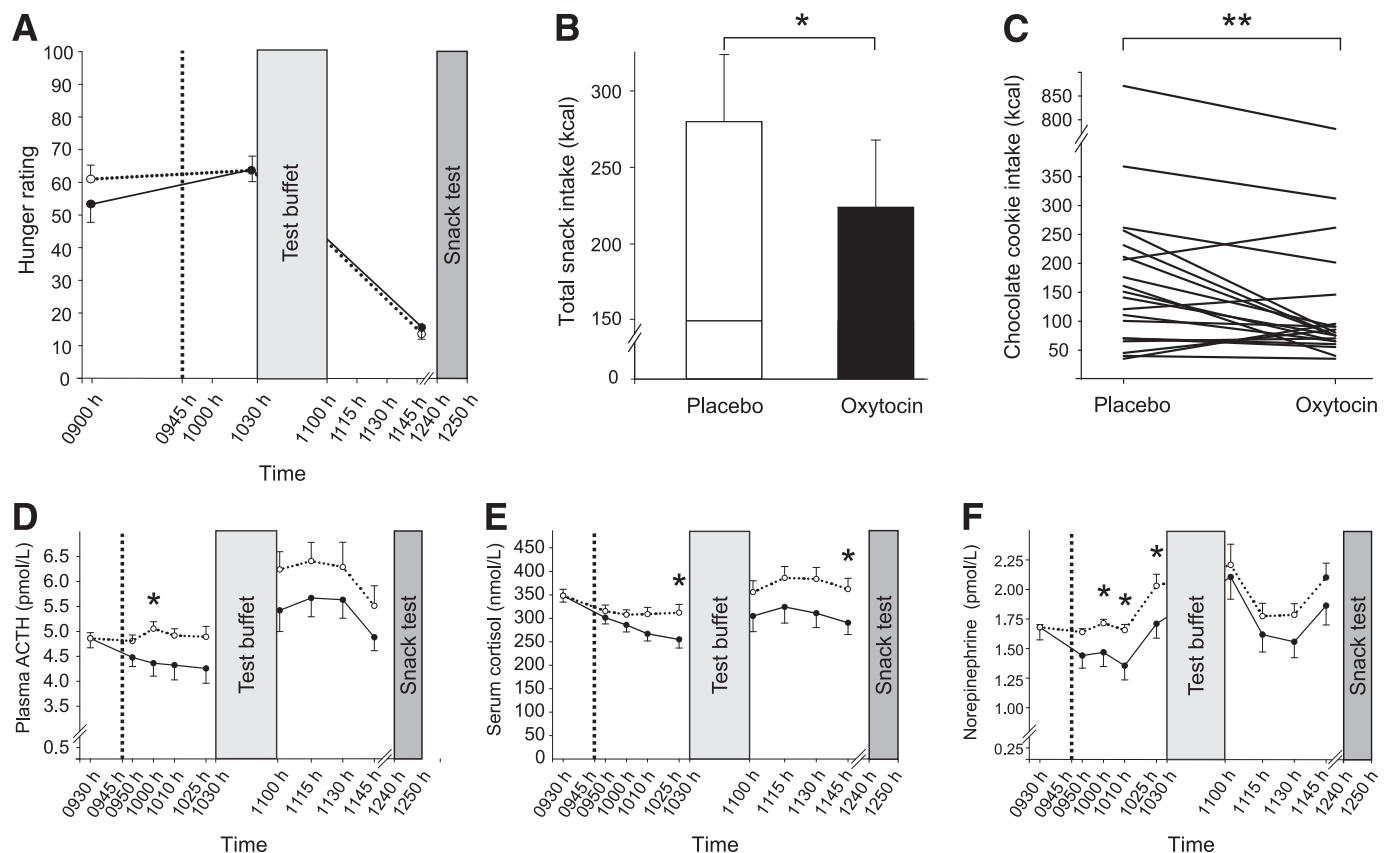


FIG. 2. Oxytocin inhibits reward-driven eating and reduces HPA axis activity. **A**: Mean  $\pm$  SEM hunger ratings assessed before (averaged across the 0915- and 0930-h baseline values) and after intranasal administration (vertical dotted line) of oxytocin (24 IU; ● and solid lines) and placebo (vehicle; ○ and dotted lines). Forty-five minutes post-treatment, subjects ate from a test breakfast (1000–1030 h) and 100 min thereafter, they ingested snacks under the pretext of a taste test (1240–1250 h). **B**: Mean  $\pm$  SEM cumulative snack intake (kcal) in the placebo (□) and the oxytocin condition (■). **C**: Individual chocolate cookie consumption assessed at the same test in the placebo and the oxytocin condition. Individual values of both sessions are connected by lines. **D–F**: Mean  $\pm$  SEM concentrations are depicted of plasma ACTH (**D**), serum cortisol (**E**), and norepinephrine (**F**) assessed before (averaged across the 0915- and 0930-h baseline values) and after oxytocin (● and solid lines) and placebo (vehicle; ○ and dotted lines) administration. Mean baseline values of both conditions are averaged to a common baseline (*n* = 20). \* $P < 0.05$ , \*\* $P < 0.01$  for comparisons between conditions (paired *t* tests).

TABLE 4  
Calorie intake and snack ratings during the snack test

	Snack type	Placebo	Oxytocin	<i>P</i> value
Intake (kcal)	Chocolate cookies	185 ± 41	138 ± 38	<b>0.007</b>
	Rice waffles	18 ± 3	13 ± 2	0.15
	Salt crackers	81 ± 19	75 ± 16	0.75
	Total	283 ± 44	227 ± 44	<b>0.03</b>
Palatability	Chocolate cookies	7.7 ± 0.28	7.45 ± 0.26	0.45
	Rice waffles	2.99 ± 0.43	3.68 ± 0.43	<b>0.05</b>
	Salt crackers	7.11 ± 0.35	7.31 ± 0.29	0.59
Sweetness	Chocolate cookies	8.06 ± 0.16	7.87 ± 0.25	0.53
	Rice waffles	0.95 ± 0.24	0.90 ± 0.29	0.88
	Salt crackers	1.55 ± 0.37	1.49 ± 0.43	0.83
Saltiness	Chocolate cookies	0.92 ± 0.31	0.92 ± 0.37	1.00
	Rice waffles	1.42 ± 0.33	1.68 ± 0.43	0.55
	Salt crackers	6.25 ± 0.44	6.79 ± 0.44	0.32

Nutritional values of the snacks are listed in Table 2. *P* values are derived from paired, two-tailed *t* tests (*n* = 20); bold type indicates statistical significance.

assumption is not supported by previous studies indicating robust central nervous effects of the peptide within 90 min after administration (3,4,28). Whereas energy expenditure remained completely unaltered, oxytocin globally attenuated HPA axis activity and blunted the peak glucose response to food intake, suggesting an insulin-sensitizing action of the peptide. These findings indicate that the

oxytocin system contributes to the control of reward-related eating as well as of stress axis regulation and glucose homeostasis in humans.

Oxytocin has been shown in a number of experiments in rodents to inhibit feeding after intracerebroventricular injection (6,8). This effect could be mimicked by the peripheral administration of high oxytocin doses that supposedly trigger hypothalamic oxytocin release in a feed-forward fashion (7,12). Furthermore, oxytocin receptor antagonists have been found to acutely hamper the anorexigenic central nervous impact of hormones such as cholecystokinin and corticotropin-releasing hormone (29,30). Vice versa,  $\alpha$ -melanocyte-stimulating hormone, a crucial player among the catabolic messengers, triggers oxytocin release from supraoptic neurons (31). Oxytocin may also induce a satiating effect by modulating distention signals from the stomach (32), but in the present experiments, we found no differences between conditions in postbreakfast hunger ratings. Considering that the anorexigenic impact of oxytocin selectively concerned the consumption of palatable snacks, it might rather be speculated that oxytocin acted on receptors expressed in the brain reward circuit, such as in the ventral tegmental area (VTA) and nucleus accumbens (33,34), that contribute to the regulation of palatable food intake (19). This conclusion should be corroborated in more mechanistically orientated experimental approaches and also in behavioral studies applying effort-based tests to assess the reward-driven motivation to obtain palatable food (35).

The attenuating effect of oxytocin on snack intake focused on chocolate cookies that were preferentially eaten by our subjects, which underlines the reward-related component of oxytocin's anorexigenic impact. Nevertheless,

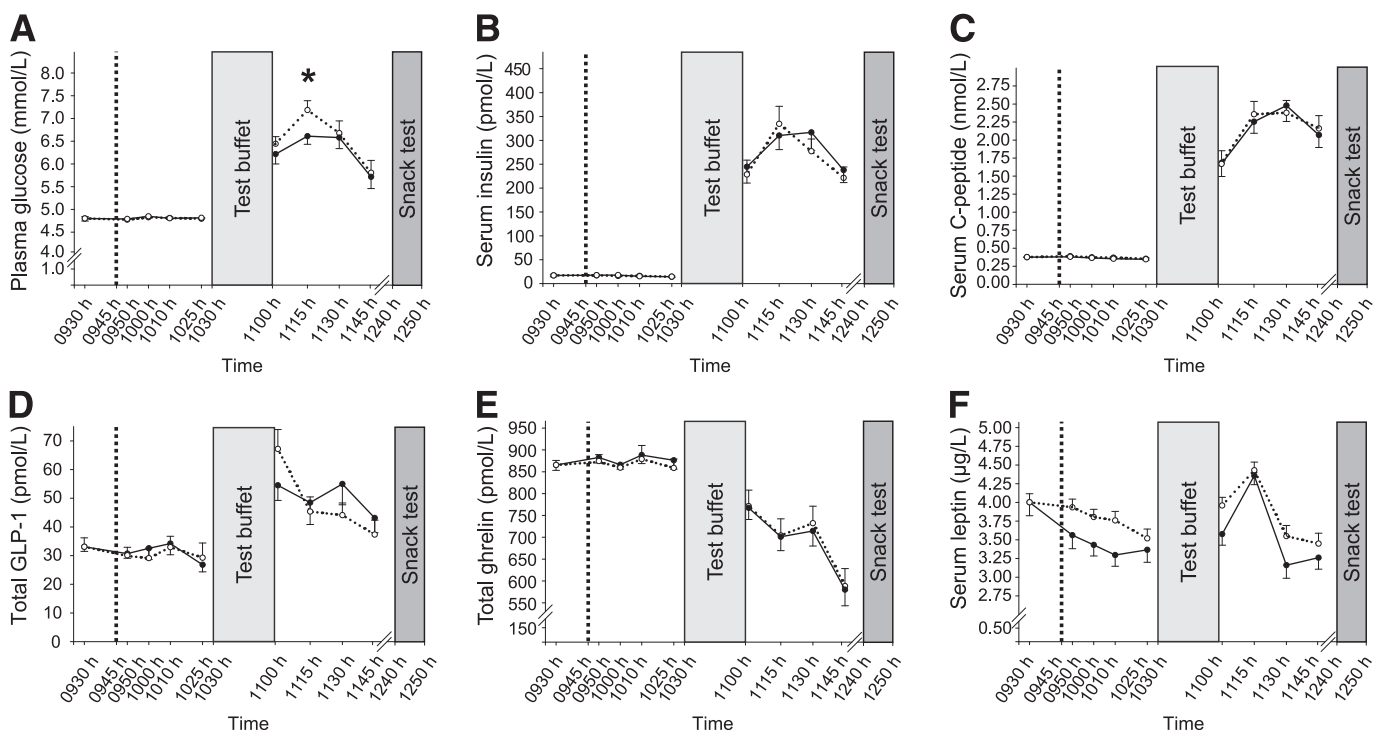


FIG. 3. Plasma glucose and hormones. Mean  $\pm$  SEM concentrations of plasma glucose (A), serum insulin (B), serum C-peptide (C), plasma total GLP-1 (D), plasma total ghrelin (E), and serum leptin (F) assessed before (averaged across the 0915- and 0930-h baseline values) and after intranasal administration (vertical dotted line) of oxytocin (24 IU;  $\bullet$  and solid lines) and placebo (vehicle;  $\circ$  and dotted lines). Subjects ate from a test breakfast from 1000 to 1030 h and ingested snacks under the pretext of a taste test from 1240 to 1250 h. Mean baseline values of both conditions are averaged to a common baseline (*n* = 20). \**P* < 0.05 for comparisons between conditions (pairwise *t* tests).



subjective ratings of chocolate and salty snacks differed in sweetness and saltiness but not palatability, suggesting that oxytocin specifically dampens the motivation to consume sweet-tasting food. In accordance, oxytocin injection into the VTA in rodents suppresses sucrose intake (36), and oxytocin signaling is strongly activated by chronic sucrose ingestion (37), whereas oxytocin-knockout animals display a preference for sucrose and carbohydrates with sweet taste (38). Oxytocin did not affect the rated palatability of chocolate cookies, which might be taken as an indication that it acted on dopaminergic pathways responding to the incentive salience of food rather than opioidergic/cannabinoid signaling assumed to process the palatability of ingested nutrients (39). Tests of olfactory function indicated that the decrease in snack intake was not mediated by effects on sensory processing. Furthermore, biasing effects on ingestive behavior related to demand characteristics and social desirability were excluded by interviews confirming unawareness of food intake measurements and by ratings of the perceived trustworthiness of the experimenter. From a clinical perspective, the conclusion that oxytocin acts on reward-processing brain circuits to suppress snack intake is in line with observations in patients with Prader-Willi syndrome, who suffer from hyperphagic obesity due to insatiable food craving and have been reported to display a 40% reduction in the number and size of oxytocin neurons (40).

The oxytocin-triggered decrease in ACTH, cortisol, and norepinephrine concentrations in the basal and postprandial state extends and refines previous findings of an attenuating impact of intravenous oxytocin on basal corticotropin function (41) and of intranasal oxytocin on HPA axis activity in response to social and physical stress (42,43) and supports the assumption that the suppression of HPA axis activity by oxytocin is mediated not only by adrenal (44) but also by central mechanisms. Acute and chronic activation of endocrine stress axes favors the intake of "comfort food" (i.e., highly palatable food) (45). In a negative feedback loop, activation of central nervous reward circuits by consuming sucrose reduces stress-induced HPA axis activity (46). The intake of sugar compared with an equicaloric fat solution induces a selective, twofold increase in hypothalamic oxytocinergic neuronal activity, whereas central nervous oxytocin receptor antagonism triggers the intake of sucrose but not fat (47). Oxytocin might impact the cross talk between reward- and stress-related pathways by modulating VTA and nucleus accumbens dopamine signaling (48) known to facilitate stress-induced HPA axis activity (49). The conclusion that the inhibition of palatable snack intake by oxytocin involves a stress axis-related component (43) is supported by the positive association between the attenuating effects of oxytocin on cortisol concentrations and chocolate cookie intake.

In addition to its dampening effect on HPA axis activity, oxytocin administration blunted the peak plasma glucose response to breakfast intake. Total calorie and macronutrient uptake from the breakfast buffet were closely comparable in both conditions, and moreover, the reduction in blood glucose concentrations was still evident after correcting the data for slight differences in these parameters. Considering that the circulating concentrations of insulin, C-peptide, and both total and active GLP-1, an incretin hormone with insulin-secretory properties, were not affected by oxytocin, this finding suggests a subtle but discernible improvement in insulin sensitivity after administration of the

peptide. Although this conclusion is in need of corroboration in experiments focusing on glucose homeostasis, it is in line with findings that oxytocin enhances insulin sensitivity and glucose tolerance in a rodent model of diet-induced obesity independent of its effects on body weight (7,50).

We found no effect of acute oxytocin administration on fasting and postprandial energy expenditure as assessed by indirect calorimetry. In diet-induced obese rats losing weight due to chronic oxytocin administration, the decrease in energy expenditure normally associated with weight loss was prevented by oxytocin treatment, probably via effects on hypothalamic thermoregulation (7). Vice versa, the ablation of oxytocin neurons favors the development of obesity by reducing energy expenditure (9). Against this background, our finding suggests that rather than exerting acute effects, oxytocin contributes to the regulation of energy expenditure on a long-term basis. Also in our experiments, oxytocin did not affect the circulating concentrations of ghrelin and GLP-1 and induced merely nonsignificant changes in leptin, hormones known to affect energy expenditure and energy homeostasis (51). Although intranasal oxytocin administration has been previously found to increase plasma concentrations of the peptide (2), this pattern moreover argues against a peripheral mediation of the observed changes in ingestive behavior.

In sum, our study provides evidence for a significant contribution of oxytocin to the control of reward-related eating behavior as well as endocrine regulation in humans. Further experiments should elucidate the preconditions and ramifications of the anorexigenic effects of oxytocin in humans by exploring the composition and timing of meals as well as the regulation of satiety in dependence of oxytocin administration. Considering recent findings that oxytocin modulates VTA activation in response to cues predicting social reward and punishment (52), its impact on the brain reward system might represent a common denominator of its psychosocial and anorexigenic properties. In concert with the dampening of stress axis activity, these effects might, for example, optimize maternal behavior during breast-feeding by isolating the mother from distracting food stimuli and preventing stress-induced inhibition of lactation (53). Excessive reward-driven food intake, chronic HPA axis activation, and insulin resistance are key factors in the pathogenesis and maintenance of obesity. With most recent clinical pilot data pointing to weight-loss inducing properties of long-term intranasal oxytocin administration in obese humans (54), the potential application of oxytocin in the treatment of metabolic disorders deserves particular attention in future research.

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V.O. and M.Ha. designed the study and wrote the manuscript. V.O. and B.H. enrolled subjects and carried out experiments for the study. V.O., G.F., B.H., and M.Ha. analyzed the data. V.O., G.F., H.L., M.He., J.B., and M.Ha. discussed the results. G.F., H.L., M.He., and J.B. contributed to writing the manuscript. M.Ha. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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